

Att. Docket No. REG 670A-US
USSN 09/868,677 filed October 1, 2001
Amendment And Response To December 7, 2001
Notification Of Missing Requirements

IN THE SPECIFICATION:

Please replace the paragraph starting on page 4, line 17, with the following:

Figures 1A-1E (SEQ ID NOS: 1 and 2)- Nucleic acid sequence (SEQ ID NO: 1) and deduced amino acid sequence (SEQ ID NO: 2) of Ang-1-FD-FD-Fc.

Please replace the paragraph starting on page 4, line 20, with the following:

Figures 2A-2E (SEQ ID NOS: 3 and 4)- Nucleic acid sequence (SEQ ID NO: 3) and deduced amino acid sequence (SEQ ID NO: 4) of Ang-2-FD-FD-Fc.

Please replace the paragraph starting on page 4, line 23, with the following:

Figures 3A-3E (SEQ ID NOS: 5 and 6)- Nucleic acid sequence (SEQ ID NO: 5) and deduced amino acid sequence (SEQ ID NO: 6) of Ang-1-FD-Fc-FD.

Please replace the paragraph starting on page 4, line 26, with the following:

Figures 4A-4E (SEQ ID NOS: 7 and 8)- Nucleic acid sequence (SEQ ID NO: 7) and deduced amino acid sequence (SEQ ID NO: 8) of Ang-2-FD-Fc-FD.

Please replace the paragraph starting on page 7, line 3, with the following:

Figures 14A-14E (SEQ ID NOS: 9 and 10)- Nucleic acid sequence (SEQ ID NO: 9) and deduced amino acid sequence (SEQ ID NO: 10) of Ephrin-B1-Ephrin-B1-Fc.

Please replace the paragraph starting on page 7, line 6, with the following:

Figures 15A-15E (SEQ ID NOS: 11 and 12)- Nucleic acid sequence (SEQ ID NO: 11) and deduced amino acid sequence (SEQ ID NO: 12) of Ephrin-B2-Ephrin-B2-Fc.

Please replace the paragraph starting on page 26, line 12, with the following:

Ang-1-FD-FD-Fc: Ang-1-FD-FD-Fc consists of a trypsin signal sequence at its amino terminus to allow for secretion (bases 1-45 of Figure 1A [SEQ ID NO: 1]) followed by the angiopoietin-1 fibrinogen domain (FD) (bases 46-690 of Figure 1A-Figure 1B [SEQ ID NO: 1]), a short bridging sequence consisting of the amino acids Gly-Pro-Ala-Pro (SEQ ID NO: 13) (bases 691-702 of Figure 1B [SEQ ID NO: 1]), a second angiopoietin-1 FD (bases 703-1750 of Figure 1B-Figure 1D [SEQ ID NO: 1]), another bridging sequence consisting of the amino acids Gly-Pro-Gly (bases 1351-1359 of Figure 1D [SEQ ID NO: 1]), and the coding sequence for the Fc portion of human IgG1 (bases 1360-2058 of Figure 1D-Figure 1E [SEQ ID NO: 1]).

Please replace the paragraph starting on page 26, line 21, with the following:

Ang-2-FD-FD-Fc: The Ang-2-FD-FD-Fc nucleic acid molecule was similarly constructed. It consists of a trypsin signal sequence (bases 1-45 of Figure 2A [SEQ ID NO: 3]), an angiopoietin-2 FD (bases 46-690 of Figure 2A- Figure 2B [SEQ ID NO: 3]), a bridging amino acid sequence Gly-Gly-Pro-Ala-Pro (SEQ ID NO: 14) (bases 691-705 of Figure 2B [SEQ ID NO: 3]), a second angiopoietin-2 FD (bases 706-1353 of Figure 2B-Figure 2D [SEQ ID NO: 3]), another bridging amino acid sequence Gly-Pro-Gly

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conf (bases 1354-1362 of Figure 2D [SEQ ID NO: 3]), and the coding sequence for the Fc portion of human IgG1 (bases 1363-2061 of Figure 2D-Figure 2E [SEQ ID NO: 3]).

Please replace the paragraph starting on page 26, line 30, through page 27, line 4, with the following:

Ang-1-FD-Fc-FD: The Ang-1-FD-Fc-FD consists of a trypsin signal sequence (bases 1-45 of Figure 3A [SEQ ID NO: 5]), an angiopoietin-1 FD (bases 46-690 of Figure 3A-3B [SEQ ID NO: 5]), the bridging amino acid sequence Gly-Pro-Gly (bases 691-699 of Figure 3B [SEQ ID NO: 5]), the coding sequence for the Fc portion of human IgG1 (bases 700-1395 of Figure 3B-3D [SEQ ID NO: 5]), another bridging amino acid sequence Gly-Gly-Gly-Gly-Ser-Gly-Ala-Pro (SEQ ID NO: 15) (bases 1396-1419 of Figure 3D [SEQ ID NO: 5]), and a second angiopoietin-1 FD (bases 1420-2067 of Figure 3D-Figure 3E [SEQ ID NO: 5]).

Please replace the paragraph starting on page 27, line 6, with the following:

Ang-2-FD-Fc-FD: The Ang-2-FD-Fc-FD nucleic acid molecule consists of a trypsin signal sequence (bases 1-45 of Figure 4A [SEQ ID NO: 7]), an angiopoietin-2 FD domain (bases 46-690 of Figure 4A-Figure 4B [SEQ ID NO: 7]), the bridging amino acid sequence Gly-Gly-Pro-Gly (SEQ ID NO: 16) (bases 691-702 of Figure 4B [SEQ ID NO: 7]), the coding sequence for the Fc portion of human IgG1 (bases 703-1398 of Figure 4B- Figure 4D [SEQ ID NO: 7]), the bridging amino acid sequence Gly-Gly-Gly-Gly-Ser-Gly-Ala-Pro (SEQ ID NO: 15) bases 1399-1422 of Figure 4D [SEQ ID NO: 7]), and a second angiopoietin-2 FD (bases 1423-2067 of Figure 4D-Figure 4E [SEQ ID NO: 7]).

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Please replace the paragraph starting on page 29, line 19, with the following:

B8
N-terminal sequencing of COS cell-derived Ang-1-FD-Fc-FD protein: Purified Ang-1-FD-Fc-FD protein was subjected to standard N-terminal sequence analysis to determine if any truncated species of the protein were being generated. This was of concern because the mutant molecule, Ang1*, has a history of containing between 10-20% N-terminally truncated species. The analysis revealed only one N-terminal sequence, Arg-Asp-X-Ala-Asp, wherein X is Cys (SEQ ID NO: 17). This sequence can be found at amino acids 16-20 of Figure 3A (SEQ ID NO: 6), and immediately follows the protein's signal sequence corresponding to amino acids 1-15 Figure 3A (SEQ ID NO: 6).

Please replace the paragraph starting on page 31, line 29, through page 32, line 3, with the following:

B9
N-terminal sequencing: Purified COS cell-derived Ang-2-FD-Fc-FD protein was subjected to standard N-terminal sequence analysis to determine if any truncated species of the protein were being generated. The analysis revealed only one N-terminal sequence, Arg-Asp-X-Ala-Glu, wherein X is Cys (SEQ ID NO: 18). This sequence can be found at amino acids 16-20 of Figure 4A (SEQ ID NO: 8), and immediately follows the protein's signal sequence corresponding to amino acids 1-15 of Figure 4A (SEQ ID NO: 8)

Please replace the paragraph starting on page 37, line 29, through page 38, 3, with the following:

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N-terminal sequencing of stable CHO clone-derived Ang-1-FD-Fc-FD protein:

B10 Purified Ang-1-FD-Fc-FD protein was subjected to standard N-terminal sequence analysis to determine if any truncated species of the protein were being generated. The analysis revealed only one N-terminal sequence, Arg-Asp-X-Ala-Asp, wherein X is Cys (SEQ ID NO: 17). This sequence can be found at amino acids 16-20 of Figure 3A (SEQ ID NO: 6) and immediately follows the protein's signal sequence corresponding to amino acids 1-15 Figure 3A (SEQ ID NO: 6).

Please replace the paragraph starting on page 39, line 9, with the following:

N-terminal sequencing of stable CHO clone-derived Ang-2-FD-Fc-FD protein:

B11 Purified stable CHO clone-derived Ang-2-FD-Fc-FD protein was subjected to standard N-terminal sequence analysis to determine if any truncated species of the protein were being generated. The analysis revealed only one N-terminal sequence, Asp-X-Ala-Glu-Val, wherein X is Cys (SEQ ID NO: 19). This sequence can be found at amino acids 17-21 of Figure 4A (SEQ ID NO: 8), and immediately follows the protein's signal sequence corresponding to amino acids 1-15 of Figure 4A (SEQ ID NO: 8)

Please replace the paragraph starting on page 41, line 24, through page 42, line 2, with the following:

B12 **(A) Ephrin-B1-Ephrin-B1-Fc:** The Ephrin-B1-Ephrin-B1-Fc DNA molecule consists of the coding sequence of the ectodomain of Ephrin-B1 (Davis et al., *ibid.*), which corresponds to nucleotides 1-711 of Figure 14A-Figure 14B (SEQ ID NO: 9), followed by a bridging sequence consisting of the amino acids Gly-Pro-Gly (nucleotides 712-

B13 cont
720 of Figure 14B [SEQ ID NO: 9], followed by a second copy of the ectodomain of Ephrin-B1 (corresponding to nucleotides 721-1344 of Figure 14B-Figure 14D [SEQ ID NO: 9]), except that in this copy of the Ephrin-B1 ectodomain the signal sequence has been removed. This second copy is followed by a second Gly-Pro-Gly amino acid bridge (nucleotides 1345-1353 of Figure 14D [SEQ ID NO: 9]), followed by the coding sequence for the Fc portion of human IgG1 (nucleotides 1354-2049 of Figure 14D-Figure 14E [SEQ ID NO: 9]).

Please replace the paragraph starting on page 42, line 4, with the following:

B13
(B) Ephrin-B2-Ephrin-B2-Fc: The Ephrin-B2-Ephrin-B2-Fc DNA molecule consists of the coding sequence of the ectodomain of Ephrin-B2 (Bergemann et al., 1995, Mol. Cell Biol. 15:4821-4929), which corresponds to nucleotides 1-675 of Figure 15A-Figure 15B (SEQ ID NO: 11), followed by a bridging sequence consisting of the amino acids Gly-Pro-Gly (nucleotides 676-684 of Figure 15B [SEQ ID NO: 11]), followed by a second copy of the ectodomain of Ephrin-B2 (corresponding to nucleotides 685-1270 of Figure 15B-Figure 15D [SEQ ID NO: 11]), except that in this copy the signal sequence has been removed. This second copy is followed by a second Gly-Pro-Gly amino acid bridge (nucleotides 1270-1278 of Figure 15D [SEQ ID NO: 11]), followed by the coding sequence for the Fc portion of human IgG1 (nucleotides 1279-1977 of Figure 15D-Figure 15E [SEQ ID NO: 11]).

Please replace the paragraph starting on page 44, line 15, with the following:

B14
The Ephrin-B2-Ephrin-B2-Fc DNA molecule consists of the coding sequence of the ectodomain of Ephrin-B2 (Bergemann et al., 1995, Mol. Cell Biol. 15:4821-4929),